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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

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MEMORANDUM

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SUBJECT: BAS510F Qualitative Risk Assessment Based On Wistar Chbb:THOM  
(SPF) Rat Dietary Studies

P.C. Code 128008

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Background

A carcinogenicity study in Wistar Chbb:THOM (SPF) rats was conducted by the Experimental Toxicology and Ecology BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, for the BASF Corporation Agricultural Products Division, Research Triangle Park, North Carolina, and dated February 28, 2001 (Laboratory Project No. 82C0179/97090, BASF Registration Document No. 2001/1000115, MRID No. 45404828).

The study design allocated groups of 50 rats per sex to dose levels of 0, 100, 500, 2500 or 15,000 ppm (0, 4.6, 23.0, 116.1 and 768.8 mg/kg/day for males; 0, 6.0, 29.7, 155.6, and 1024.4 mg/kg/day for females) of BAS510F for 105 weeks. The 15,000 ppm dose group exhibited mortality in males and excessive weight loss in females and, therefore, this dose group was terminated at 17 months and not further analyzed.

A chronic toxicity study in Wistar Chbb:THOM (SPF) rats was conducted by the Experimental Toxicology and Ecology BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, for the BASF Corporation Agricultural Products Division, Research Triangle Park, North Carolina, and dated February 28, 2001 (Laboratory Project No. 82C0179/97091, BASF Registration Document No. 2001/1000114, MRID No. 45404827).

The study design allocated groups of 20 rats per sex to dose levels of 0, 100, 500, 2500 or 15,000 ppm (0, 4.4, 21.9, 110.0 and 739.0 mg/kg/day for

males; 0, 5.9, 30.0, 150.3, and 1000.4 mg/kg/day for females) of BAS510F for 105 weeks. Both sexes in the 15,000 ppm dose group exhibited excessive weight loss and, therefore, these animals were terminated at 17 months and not further analyzed.

#### Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of BAS510F in either male or female rats of the carcinogenicity study, or in male rats of the chronic toxicity study. Female rats of the chronic toxicity study indicated a statistically significant decreasing trend for mortality, as well as a statistically significant pair-wise comparison of the high dose with the control. Though there were survival disparities among the dose groups for the female rats of the chronic toxicity study, there were too few animals in this study to appropriately use the Peto's Prevalence test, since the first tumor was observed at week 102. The Fisher's Exact test and the exact test for trend were used for all mortality analyses. See Tables 1, 4 and 6 for male mortality test results. See Tables 9, 12 and 14 for female mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

#### Tumor Analyses: Carcinogenicity Study

Male rats had significant increasing trends in thyroid follicular cell adenomas at  $p < 0.01$ , and adenomas and/or carcinomas combined at  $p < 0.05$ . There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Female rats had a significant increasing trend in thyroid follicular cell adenomas at  $p < 0.05$ . There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of both sexes were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 2, 3, 10 and 11 for carcinogenicity study tumor analysis results.

#### Tumor Analyses: Chronic Toxicity Study

There were no statistically significant trends or pair-wise comparisons of the dosed groups with the controls in either male or female rats of the chronic toxicity study.

The statistical analyses of both sexes were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 5 and 13 for chronic toxicity study tumor analysis results.

#### Tumor Analyses: Carcinogenicity and Chronic Toxicity Studies Combined

Male rats had significant increasing trends in thyroid follicular cell adenomas at  $p < 0.01$ , and adenomas and/or carcinomas combined at  $p < 0.05$ . There was a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls for thyroid follicular cell adenomas at  $p < 0.05$ .

Female rats had a significant increasing trend for thyroid follicular cell adenomas at  $p < 0.05$ . There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of both sexes were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 7, 8, 15, and 16 for carcinogenicity and chronic toxicity studies combined tumor analysis results.

4

Table 1. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Male Mortality Rates\* and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-108 <sup>†</sup>	
0	0/50	0/50	2/50	7/48	9/50 (18)
100	0/50	0/50	2/50	11/48	13/50 (26)
500	0/50	0/50	2/50	11/48	13/50 (26)
2500	0/50	0/50	2/50	14/48	16/50 (32)

\*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>†</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

4

5

Table 2. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Male Thyroid Follicular Cell Tumor Rates\* and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas (%)	0/50 (0)	0/50 (0)	1/50 (2)	4*/50 (8)
p =	0.0054**	1.0000	0.5000	0.0587
Carcinomas (%)	1 <sup>b</sup> /50 (2)	0/50 (0)	0/50 (0)	0/50 (0)
p =	0.2500	0.5000	0.5000	0.5000
Combined (%)	1/50 (2)	0/50 (0)	1/50 (2)	4/50 (8)
p =	0.02145*	0.5000	0.7525	0.1811

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

\*First adenoma observed at week 87, dose 2500 ppm.

<sup>b</sup>First carcinoma observed at week 107, dose 0 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

5

6

Table 3. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Male Thyroid C-Cell Tumor Rates\* and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas	5/50	5 <sup>a</sup> /50	6/50	3/50
(%)	(10)	(10)	(12)	(6)
p =	0.2019	0.6297	0.5000	0.3575
Carcinomas	0/50	2 <sup>b</sup> /50	0/50	1/50
(%)	(0)	(4)	(0)	(2)
p =	0.4384	0.2475	1.0000	0.5000
Combined	5/50	7/50	6/50	4/50
(%)	(10)	(14)	(12)	(8)
p =	0.2423	0.3798	0.5000	0.5000

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

<sup>a</sup>First adenoma observed at week 84, dose 100 ppm.

<sup>b</sup>First carcinoma observed at week 72, dose 100 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

6

7

Table 4. BAS510F - Wistar Chbb:THOM (SPF) Chronic Toxicity Rat Study

Male Mortality Rates<sup>a</sup> and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-106 <sup>f</sup>	
0	0/20	0/20	0/20	5/20	5/20 (25)
100	0/20	0/20	1/20	3/19	4/20 (20)
500	0/20	0/20	2/20	4/18	6/20 (30)
2500	0/20	0/20	1/20	5/19	6/20 (30)

<sup>a</sup>Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>f</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

7

8

Table 5. BAS510F - Wistar Chbb:THOM (SPF) Chronic Toxicity Rat Study

Male Thyroid Tumor Rates\* and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
C-Cell				
Adenomas#	4/20	2/20	3 <sup>a</sup> /20	4/20
(%)	(20)	(10)	(15)	(20)
p =	0.3274	0.3307	0.5000	0.6526
Follicular				
Cell				
Adenomas#	0/20	0/20	2 <sup>b</sup> /20	1/20
(%)	(0)	(0)	(10)	(5)
p =	0.1989	1.0000	0.4949	0.5000

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

<sup>a</sup>First c-cell adenoma observed at week 79, dose 500 ppm.

<sup>b</sup>First follicular cell adenoma observed at week 105, dose 500 ppm.

#No c-cell or follicular cell carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

8



9

Table 6. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Male Mortality Rates\* and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-108 <sup>f</sup>	
0	0/70	0/70	2/70	12/68	14/70 (20)
100	0/70	0/70	3/70	14/67	17/70 (24)
500	0/70	0/70	4/70	15/66	19/70 (27)
2500	0/70	0/70	3/70	19/67	22/70 (31)

\*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>f</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

9

10

Table 7. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Male Thyroid Follicular Cell Tumor Rates\* and Exact Trend Test and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas (%)	0/70 (0)	0/70 (0)	3/70 (4)	5*/70 (7)
p =	0.0045**	1.0000	0.1223	0.0290*
Carcinomas (%)	1 <sup>b</sup> /70 (1)	0/70 (0)	0/70 (0)	0/70 (0)
p =	0.2500	0.5000	0.5000	0.5000
Combined (%)	1/70 (1)	0/70 (0)	3/70 (4)	5/70 (7)
p =	0.0130*	0.5000	0.3098	0.1043

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

\*First adenoma observed at week 87, dose 2500 ppm.

<sup>b</sup>First carcinoma observed at week 107, dose 0 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

10

11

Table 8. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Male Thyroid C-Cell Tumor Rates\* and Exact Trend Test and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas (%)	9/70 (13)	7/70 (10)	9 <sup>a</sup> /70 (13)	7/70 (10)
p =	0.3625	0.3957	0.5993	0.3957
Carcinomas (%)	0/70 (0)	2 <sup>b</sup> /70 (3)	0/70 (0)	1/70 (1)
p =	0.4382	0.2482	1.0000	0.5000
Combined (%)	9/70 (13)	9/70 (13)	9/70 (13)	8/70 (11)
p =	0.3927	0.5993	0.5993	0.5000

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

<sup>a</sup>First adenoma observed at week 79, dose 500 ppm.

<sup>b</sup>First carcinoma observed at week 72, dose 100 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

11

12

Table 9. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Female Mortality Rates\* and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-107 <sup>†</sup>	
0	0/50	0/50	2/50	12/48	14/50 (28)
100	0/50	0/50	2/50	6/48	8/50 (16)
500	0/50	1/50	1/49	9/48	11/50 (22)
2500	0/50	0/50	1/50	9/49	10/50 (20)

\*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>†</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

12

13

Table 10. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Female Thyroid Follicular Cell Tumor Rates\* and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas*	0/50	1*/50	0/49	3/50
(%)	(0)	(2)	(0)	(6)
p =	0.0342*	0.5000	1.0000	0.1212

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

\*First adenoma observed at week 106, dose 100 ppm.

\*No carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

13

14

Table 11. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity Rat Study

Female Thyroid C-Cell Tumor Rates and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas	8/50	8/50	7 <sup>a</sup> /49	5/50
(%)	(16)	(16)	(14)	(10)
p =	0.1664	0.6071	0.5171	0.2768
Carcinomas	0/50	0/50	1 <sup>b</sup> /49	0/50
(%)	(0)	(0)	(2)	(0)
p =	0.7487	1.0000	0.4949	1.0000
Combined	8/50	8/50	8/49	5/50
(%)	(16)	(16)	(16)	(10)
p =	0.1566	0.6071	0.5900	0.2768

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

<sup>a</sup>First adenoma observed at week 77, dose 500 ppm.

<sup>b</sup>First carcinoma observed at week 105, dose 500 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

14

15

Table 12. BAS510F - Wistar Chbb:THOM (SPF) Chronic Toxicity Rat Study

Female Mortality Rates<sup>a</sup> and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-106 <sup>b</sup>	
0	0/20	0/20	1/20	6/19	7/20 (35)*
100	0/20	0/20	0/20	3/20	3/20 (15)
500	0/20	0/20	1/20	6/19	7/20 (35)
2500	0/20	0/20	1/20	0/19	1/20 (5)*

<sup>a</sup>Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>b</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

16

Table 13. BAS510F - Wistar Chbb:THOM (SPF) Chronic Toxicity Rat Study

Female Thyroid Tumor Rates\* and Exact Trend Test  
and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
C-Cell Adenomas#	3/20	5 <sup>a</sup> /20	7/20	4/20
(%)	(15)	(25)	(35)	(20)
p =	0.4434	0.3474	0.1367	0.5000
Follicular Cell Adenomas#	0/20	0/20	1 <sup>b</sup> /20	0/20
(%)	(0)	(0)	(10)	(0)
p =	0.7500	1.0000	0.5000	1.0000

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

<sup>a</sup>First c-cell adenoma observed at week 102, dose 100 ppm.

<sup>b</sup>First follicular cell adenoma observed at week 106, dose 500 ppm.

#No c-cell or follicular cell carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

16



17

Table 14. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Female Mortality Rates<sup>†</sup> and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-107 <sup>‡</sup>	
0	0/70	0/70	3/70	18/67	21/70 (30)
100	0/70	0/70	2/70	9/68	11/70 (16)*
500	0/70	1/70	2/69	15/67	18/70 (26)
2500	0/70	0/70	2/70	9/68	11/70 (16)*

\*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>‡</sup>Final sacrifice at week 105.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

18

Table 15. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Female Thyroid Follicular Cell Tumor Rates\* and Exact Trend Test and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas <sup>a</sup>	0/70	1 <sup>a</sup> /70	1 <sup>a</sup> /69	3/70
(%)	(0)	(1)	(1)	(4)
p =	0.0439 <sup>*</sup>	0.5000	0.4964	0.1223

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

\*First adenomas observed concurrently at week 106 at doses 100 and 500 ppm.

\*No carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

18

19

Table 16. BAS510F - Wistar Chbb:THOM (SPF) Carcinogenicity and Chronic Toxicity Combined Rat Studies

Female Thyroid C-Cell Tumor Rates\* and Exact Trend Test and Fisher's Exact Test Results (p-values)

	<u>Dose (ppm)</u>			
	0	100	500	2500
Adenomas (%)	11/70 (16)	13/70 (19)	14*/69 (20)	9/70 (13)
p =	0.1903	0.4115	0.3153	0.4049
Carcinomas (%)	0/70 (0)	0/70 (0)	1 <sup>b</sup> /69 (1)	0/70 (0)
p =	0.7491	1.0000	0.4964	1.0000
Combined (%)	11/70 (16)	13/70 (19)	15/69 (22)	9/70 (13)
p =	0.1803	0.4115	0.2443	0.4049

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

\*First adenoma observed at week 77, dose 500 ppm.

<sup>b</sup>First carcinoma observed at week 105, dose 500 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

19

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